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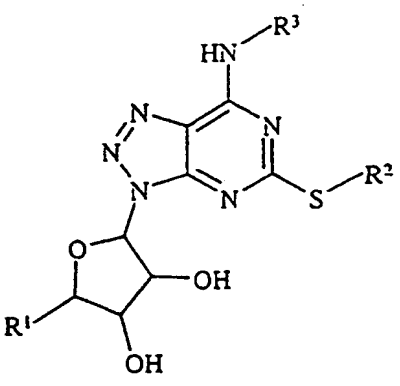
(54) Title: NOVEL RIBOSE COMPOUNDS



(I)

(57) Abstract: The invention provides novel ribose compounds of formula (I); their use as medicaments, compositions containing them and processes for their preparation.

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NOVEL RIBOSE COMPOUNDS

FIELD OF THE INVENTION

The present invention provides novel ribose analogues, their use as medicaments, compositions containing them and processes for their preparation.

BACKGROUND OF THE INVENTION

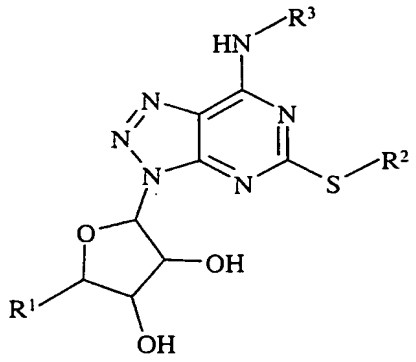
Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and platelet-mediated occlusion or re-occlusion also compromises angioplasty.

A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross-linking of platelets by binding of fibrinogen to a membrane-binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), *Circulation* **90**, pp. 1624-1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators (1994) *Circulation* **90**, pp. 1631-1637; Neuhaus K. L. et. al. (1994) *Circulation* **90**, pp. 1638-1642).

It has been found that ADP acts as a key mediator of thrombosis. ADP-induced platelet aggregation is mediated by the P_{2T} receptor subtype located on the platelet membrane. The P_{2T} receptor (also known as $P2Y_{ADP}$ or $P2T_{AC}$) is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., *Br. J. Pharmacology,* (1994), **113**, 1057-1063, and Fagura et al., *Br. J. Pharmacology* (1998) **124**, 157-164. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents (see *J. Med. Chem.* (1999) **42**, 213). There is a need to find P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists as anti-thrombotic agents.

DESCRIPTION OF THE INVENTION

In a first aspect the invention provides a compound of formula (I):



(I)

wherein:

R^1 is either alkyl C_{1-6} substituted by OH or COR^4;

R^2 is alkyl C_{1-6} or haloalkyl C_{1-6};

R^3 is cycloalkyl C_{3-6} optionally substituted by R^5;

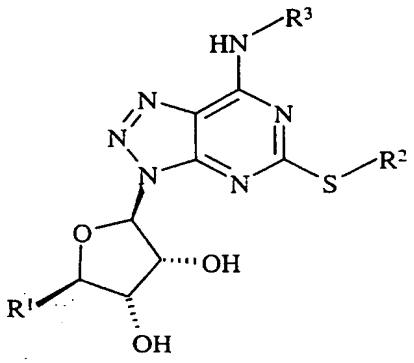
R^4 is OR^6 or NHR^6;

R^5 is phenyl optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen and OR^6;

R^6 is H or alkyl C_{1-6};

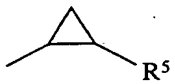
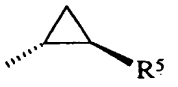
or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

Preferably the compound of formula (I) has the following stereochemistry:



(Ia)

where R^1, R^2 and R^3 are as defined above

When R^3 is  , where R^5 is defined above, the stereochemistry is preferably 

Suitably, R^1 is CH_2OH, $(CH_2)_2OH$, COOH or CONHEt.

Suitably, R^2 is alkyl C_3 optionally substituted by three halogen atoms.

Particularly preferred compounds of the invention include:

(1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-[2-(4-Chlorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-[2-(4-Fluorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(3,3,3-trifluoropropylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-3-(5-Deoxy-β-D-*ribo*-hexofuranosyl)-*N*-(2-phenylcyclopropyl)-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

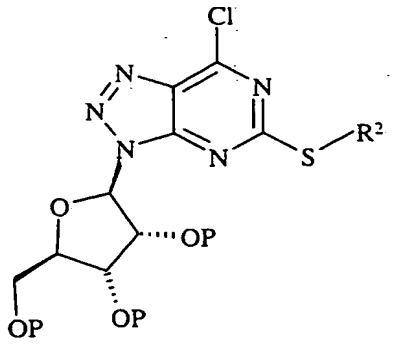
(1*R-trans*)-1-Deoxy-1-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronic acid;

(1*R-trans*)-1-Deoxy-*N*-ethyl-1-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronamide;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises:

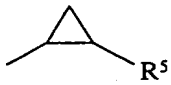
a. For compounds of formula (I) where R^1 is CH_2OH, reacting a compound of formula (II):



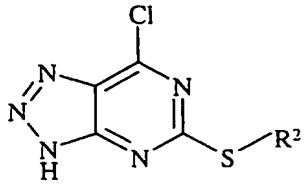
(II)

where R^2 is defined above and P is a protecting group, preferably benzoyl, with R^3NH_2, where R^3 is defined above, and a base, preferably triethylamine or *N,N*-diisopropylethylamine, in the presence of dipolar aprotic solvent, preferably *N,N*-dimethylformamide or an alcohol, preferably n-butanol, at a temperature between about 100 and about 150°C, and optionally thereafter removing any protecting groups.

Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

When R^3 is  and when R^5 is phenyl, it may be prepared as described in L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044. When R^5 is phenyl substituted by one or more groups selected from C_{1-6} alkyl, halogen and OR^6 it may be prepared as described in International Patent Application WO 9905143.

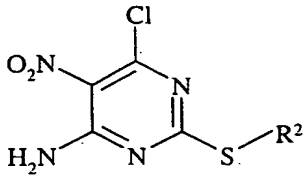
A compound of formula (II) can be prepared by reacting a compound of formula (III):



(III)

where R^2 is defined above, with 1-*O*-acetyl-2,3,4-tri-*O*-benzoyl-β-D-ribofuranose and an acid, preferably *p*-toluenesulphonic acid, at a temperature between about 100 and about 150°C.

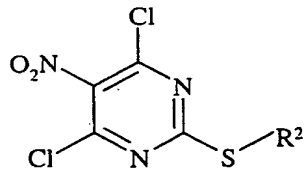
A compound of formula (III) can be prepared by reducing a compound of formula (IV):



(IV)

where R^2 is defined above, with a metal, preferably iron powder, in the presence of an acid, preferably acetic acid, followed by diazotization using a C_{1-6} alkyl nitrite, preferably iso-amyl nitrite, in the presence of an inert dipolar aprotic solvent, preferably acetonitrile, at a temperature between about 20 and about 100°C.

A compound of formula (IV) can be prepared by reacting a compound of formula (V):

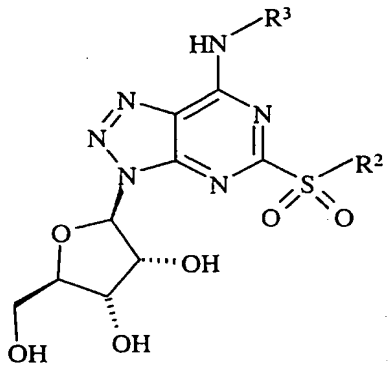


(V)

where R^2 is defined above, with aqueous ammonia in the presence of an inert ethereal solvent, preferably 1,4-dioxane, at a temperature between about 0 and about 50°C.

The compound of formula (V) may be prepared as described in International Patent Application WO 9828300.

b. For compounds of formula (I) where R^1 is CH_2OH, interconverting R^2 by reacting a compound of formula (VI):



(VI)

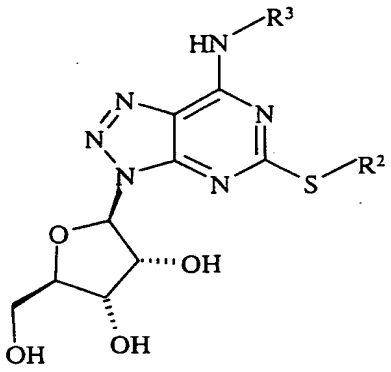
where R^2 and R^3 are as defined above,

i) with sodium hydrosulphide (NaSH) in the presence of a dipolar aprotic solvent, preferably *N,N*-dimethylformamide, at a temperature between about 0 and about 50°C and treating the product of this reaction with an alkyl halide ($R^{2'}X$), preferably 1-bromo-3,3,3-trifluoropropane, in the presence of a dipolar aprotic solvent, preferably *N,N*-dimethylformamide, at a temperature between about 0 and about 50°C, or

ii) with a sodium alkylthiolate ($R^{2'}SNa$) in the presence of a dipolar aprotic solvent, preferably *N,N*-dimethylformamide, at a temperature between about 0 and about 50°C,

where $R^{2'}$ is different from the R^2 being interconverted.

A compound of formula (VI) may be made by the oxidation of a compound of formula (VII):

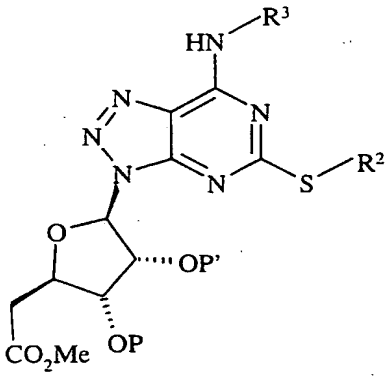


(VII)

where R^2 and R^3 are as defined above, with a peracid, preferably *m*-chloroperoxybenzoic acid, in the presence of a chlorocarbon solvent, preferably dichloromethane, at a temperature between about 0 and about 50°C.

The preparation of the compound of formula (VII) was described above in step a.

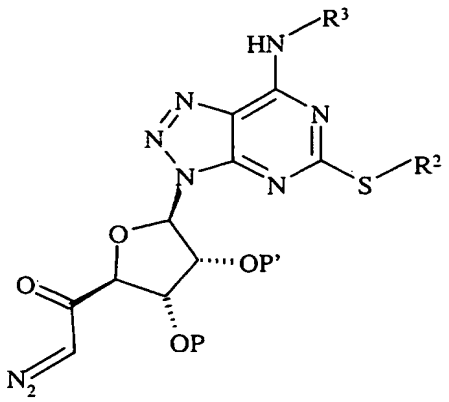
c. For compounds of formula (I) where R^1 is $(CH_2)_2OH$, reducing a compound of formula (VIII):



(VIII)

where P and P' are protecting groups, preferably CMe_2, and R^2 and R^3 are as defined above, with a metal hydride, preferably di-isobutylaluminiumhydride, in the presence of an inert solvent, preferably toluene, at a temperature between about 0 and about 50°C and optionally thereafter removing any protecting groups. Preferably the protecting groups are removed by reaction with trifluoroacetic acid, using water or aqueous acetonitrile as solvents, at a temperature between about 0 and about 100°C.

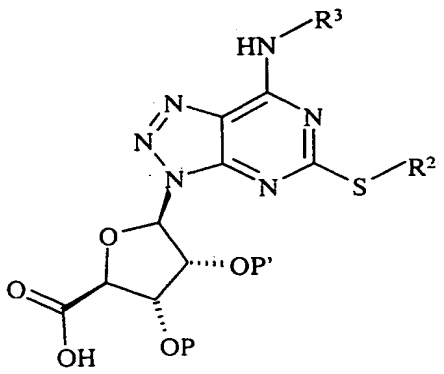
A compound of formula (VIII) can be made by reacting a compound of formula (IX):



(IX)

where P, P', R^2 and R^3 are as defined above, with silver (I) oxide in the presence of an alcohol, preferably methanol, at a temperature between about 20 and about 80°C.

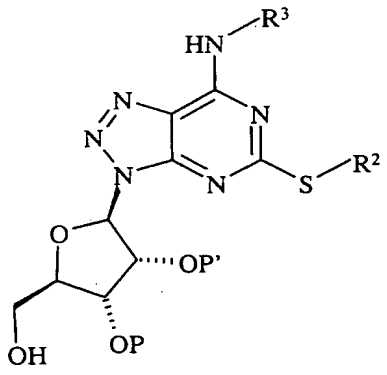
A compound of formula (IX) can be made by reacting a compound of formula (X):



(X)

where P, P', R^2 and R^3 are as defined above, with an alkylchloroformate, preferably iso-butylchloroformate, in the presence of a base, preferably *N*-methylmorpholine, followed by reaction with diazomethane in the presence of an ethereal solvent, preferably a mixture of tetrahydrofuran and diethylether, at a temperature between about -10 and about 20°C

A compound of formula (X) can be made by oxidising a compound of formula (XI):



(XI)

where P, P', R^2 and R^3 are as defined above, preferably with pyridinium dichromate, in the presence of an inert dipolar aprotic solvent, preferably *N,N*-dimethylformamide, at a temperature between about 0 and about 50°C.

A compound of formula (XI) can be made by reacting a compound of formula (VII) with a ketal or acetal, preferably 2,2-dimethoxypropane in acetone, and an acid, preferably *p*-toluenesulphonic acid, at a temperature between about 0 and about 100°C. The preparation of the compound of formula (VII) was described above.

d. For compounds of formula (I) where R^1 is COOH, deprotecting a compound of formula (X) using an acid, preferably trifluoroacetic acid, in water or aqueous acetonitrile, at a temperature between about 0 and about 100°C.

e. For compounds of formula (I) where R^1 is $CONHR^6$, activating the carboxylic group of a compound of formula (X) with a suitable activating reagent, preferably benzotriazolyl-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, and reaction with R^6NH_2, where R^6 is defined above, in the presence of a base, preferably *N,N*-di-isopropylethylamine in inert ethereal solvent, preferably tetrahydrofuran, at a temperature between about 0 and about 50°C and optionally thereafter removing any protecting groups. Preferably the protecting groups are removed using trifluoroacetic acid in water or aqueous acetonitrile at a temperature between about 0 and about 100°C.

Compounds of formulae (II), (VI), (VII), (VIII) and (X) form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, tetrahydrofuran or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may be

carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

The compounds of the invention act as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor antagonists. Accordingly, the compounds are useful in therapy, including combination therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary revascularisation procedures including angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation *in vivo*, such as cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as

asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process. Further indications include treatment of CNS disorders and prevention of the growth and spread of tumours.

According to the invention there is further provided the use of a compound according to the invention as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of the above disorders. In particular the compounds of the invention are useful for treating myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and stable and unstable angina, especially unstable angina. The invention also provides a method of treatment or prevention of the above disorders which comprises administering a therapeutically effective amount of a compound according to the invention to a person suffering from or susceptible to such a disorder.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a

dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres, which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution, which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol, mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

EXAMPLES

The invention is illustrated by the following non-limiting examples.

In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, FAB spectra were obtained on a VG70-250SEQ spectrometer, ESI and APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a Novapak®, Bondapak® or Hypersil® column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO_2)) was carried out using Fisher Matrix silica, 35-70 μm. For examples which showed the presence of rotamers in the proton NMR spectra only the chemical shifts of the major rotamer are quoted.

Example 1

(1*R*-*trans*)-*N*-(2-Phenylcyclopropyl)-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

a) 6-Chloro-5-nitro-2-(propylthio)pyrimidin-4-amine

A stirred solution of 4,6-dichloro-5-nitro-2-(propylthio)pyrimidine (prepared as described in WO9828300) (2.6g) in 1,4-dioxane (50ml) was treated with concentrated ammonia solution (1ml) at room temperature for 24 hours. The reaction mixture was concentrated *in vacuo* and the residue triturated with hexane to give the sub-title compound (2.2g).

MS (APCI) 247/9 ($M-H^+$, 100%).

b) 7-Chloro-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine

Iron powder (5g) was added in portions over 2 hours to a solution of the product from step a) (5g) in acetic acid (200ml) at 25 °C and the suspension stirred for a further 2 hours. The reaction mixture was neutralised with sodium bicarbonate solution and extracted with dichloromethane. The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. The resultant oil was dissolved in acetonitrile (25ml), isoamyl nitrite (7.5ml) added and the solution stirred at 65 °C for 1 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, dichloromethane followed by ethyl acetate as eluants) to give the sub-title compound (5g).

MS (APCI) 228/30 ($M+H^+$, 100%).

c) 2,3,5-Tri-*O*-benzoyl-1-deoxy-1-[7-chloro-5-(propylthio)-3*H* -[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-β-D-ribofuranose (together with 2,3,5-tri-*O*-benzoyl-1-deoxy-1-[7-chloro-5-(propylthio)-3*H* -[1,2,3]-triazolo[4,5-d]pyrimidin-2-yl]-β-D-ribofuranose and 2,3,5-tri-*O*-benzoyl-1-deoxy-1-[7-chloro-5-(propylthio)-3*H* -[1,2,3]-triazolo[4,5-d]pyrimidin-1-yl]-β-D-ribofuranose)

A mixture of the product from step b) (8g), 1-*O*-acetyl-2,3,4-tri-*O*-benzoyl-β-D-ribofuranose (16g) and *p*-toluenesulphonic acid were heated together *in vacuo* at 120°C for 30 minutes. The cooled reaction mixture was purified by chromatography (SiO_2,

dichloromethane:ethyl acetate 9:1 as eluant) to give the sub-title compound (15g) as the major fraction in a mixture of isomers (used without further purification).

d) (1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(propylthio)-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)]-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

A mixture of the products from step c) (3.37 g), (1*R-trans*)-2-phenylcyclopropylamine [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044) (1.5g) and diisopropylethylamine (3 ml) in dichloromethane (60 ml) was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the sub-title compound (3.4 g).

MS (APCI) 771 ($M+H^+$, 100%).

e) (1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

A mixture of the product from step a) (3 g) and sodium methoxide (1g) in methanol (20ml) was stirred 25 °C for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, dichloromethane followed by methanol:dichloromethane 1:9 as eluants) to afford the title compound (1g).

MS (APCI) 459 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.4 (1H, d), 7.41-7.10 (5H, m), 6.06 (1H, d), 5.55 (1H, d), 5.26 (1H, d), 4.83-4.80 (2H, m), 4.29-4.25 (1H, m), 3.98 (1H, m), 3.60-3.58 (1H, m), 3.50-3.44 (1H, m), 3.21 (1H, m), 3.00-2.80 (2H, m), 2.25-2.1 (2H, m), 1.80-1.30 (3H, m), 0.90 (3H, t).

Example 2

(1*R-trans*)-*N*-[2-(4-Chlorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

a) (1*R-trans*)-*N*-[2-(4-Chlorophenyl)cyclopropyl]-5-(propylthio)-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

The sub-title compound was prepared by the method of example 1, step d) using (1*R-trans*)-2-(4-chlorophenyl)cyclopropylamine (prepared as described in International Patent Application WO 9905143).

MS (APCI) 805 ($M+H^+$, 100%).

b) (1*R-trans*)-*N*-[2-(4-Chlorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

The title compound was prepared by the method of example 1, step e) using the product from step a).

MS (APCI) 493 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.5 (1H, d), 7.34-7.33 (2H, d), 7.24-7.21 (2H, d), 6.06 (1H, d), 5.58 (1H, d), 5.26 (1H, d), 4.83-4.80 (2H, m), 4.29-4.25 (1H, m), 3.98 (1H, m), 3.60-3.58 (1H, m), 3.50-3.40 (1H, m), 3.21 (1H, m), 3.00-2.80 (2H, m), 2.20-2.10 (1H, m), 1.80-1.30 (4H, m), 0.80 (3H, t)

Example 3

(1*R-trans*)-*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

a) (1*R-trans*)-*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-5-(propylthio)-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

The sub-title compound was prepared by the method of example 1 step d) using (1*R-trans*)-2-(3,4-difluorophenyl)cyclopropylamine [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described in International Patent Application WO 9905143).

MS (APCI) 806 ($M+H^+$, 100%).

b) (1*R-trans*)-*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

The title compound was prepared by the method of example 1, step e) using the product from step a).

MS (APCI) 495 ($M+H^+$, 100%)

NMR δH ($CDCl_3$ + d_6-DMSO) 8.05 (1H, d), 7.14-6.90 (3H, d), 6.36 (1H, d), 5.18-5.14 (1H, d), 4.96-4.90 (1H, m), 4.68-4.64 (1H, m), 4.5 (1H, s), 4.39 (1H, d), 4.29-4.25 (1H, m), 4.0-3.90 (1H, m), 3.80-3.70 (1H, m), 3.21 (1H, m), 3.10-2.80 (2H, m), 2.20-2.10 (1H, m), 1.60-1.30 (4H, m), 0.80 (3H, t)

Example 4

(1*R-trans*)-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

a) (1*R-trans*)-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-5-(propylthio)-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

The sub-title compound was prepared by the method of example 1, step d) using (1*R-trans*)-2-(4-methoxyphenyl)cyclopropylamine [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described in International Patent Application WO 9905143).

MS (APCI) 801 ($M+H^+$, 100%).

b) (1*R-trans*)-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

The title compound was prepared by the method of example 1, step e) using the product from step a).

MS (APCI) 489 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.4 (1H, d), 7.15-7.10 (2H, d), 6.87-6.85 (2H, d), 6.06 (1H, d), 5.55 (1H, d), 5.26 (1H, d), 4.83-4.80 (2H, m), 4.29-4.25 (1H, m), 3.98 (1H, m), 3.72 (3H, s), 3.60-3.58 (1H, m), 3.58-3.44 (1H, m), 3.12-3.10 (1H, m), 3.0-2.85 (2H, m), 2.15-2.07 (1H, m), 1.80-1.20 (4H, m), 0.84 (3H, t).

Example 5

(1*R-trans*)-*N*-[2-(4-Fluorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

a) (1*R-trans*)-*N*-[2-(4-Fluorophenyl)cyclopropyl]-5-(propylthio)-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

The sub-title compound was prepared by the method of example 1, step d) using (1*R-trans*)-2-(4-fluorophenyl)cyclopropylamine (prepared as described in International Patent Application WO 9905143).

MS (APCI) 789 ($M+H^+$, 100%).

b) (1*R-trans*)-*N*-[2-(4-Fluorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

The title compound was prepared by the method of example 1, step e) using the product from step a).

MS (APCI) 477 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.4 (1H, d), 7.35-7.20 (2H, d), 7.15-7.10 (2H, d), 6.70 (1H, d), 5.55 (1H, d), 5.26 (1H, d), 4.85-4.80 (2H, m), 4.29-4.25 (1H, m), 3.98 (1H, m), 3.65-3.58 (1H, m), 3.50-3.40 (1H, m), 3.20-3.00 (1H, m), 3.00-2.80 (2H, m), 2.20-2.10 (1H, m), 1.80-1.20 (4H, m), 0.84 (3H, t).

Example 6

(1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(3,3,3-trifluoropropylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

a) (1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(propylsulphonyl)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

A mixture of the product from example 1 (0.6g) and *m*-chloroperbenzoic acid (0.9g) was stirred in dichloromethane (20ml) solution for 1 hour. The reaction mixture was washed with aqueous sodium bicarbonate and the organic phase concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the sub-title compound (0.6 g).

MS (APCI) 491 ($M+H^+$, 100%).

b) (1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(3,3,3-trifluoropropylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

To the product from step a) (0.5g) in dimethylformamide (5ml) solution was added sodium hydrosulphide (0.2g) over 15 minutes. 1-Bromo-3,3,3-trifluoropropane (1ml) was added and the mixture stirred for 4 hours at 25 °C. Water was added and the product extracted into ethyl acetate. The organic phase was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the title compound (0.1g).

MS (APCI) 513 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.54 (1H, d), 7.31-7.10 (5H, m), 6.07 (1H, d), 5.55 (1H, d), 5.26 (1H, d), 4.85-4.80 (2H, m), 4.25-4.07 (1H, m), 4.00-3.95 (1H, m), 3.60-3.50 (1H, m), 3.50-3.40 (1H, m), 3.30-3.00 (3H, m), 2.30-2.21 (2H, m), 1.80-1.20 (3H, m).

Example 7

(1*R-trans*)-3-(5-Deoxy-β-D-*ribo*-hexofuranosyl)-*N*-(2-phenylcyclopropyl)-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

a) (1*R-trans*)-3-[2,3-*O*-(1-Methylethylidene)-β-D-ribofuranosyl]-*N*-(2-phenylcyclopropyl)-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

To a solution of (1*R-trans*)-*N*-(2-phenylcyclopropyl)-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine (prepared as described in Example 1) (3.1g) in dry acetone was added 2,2-dimethoxypropane (8ml) followed by *p*-toluenesulphonic acid (1.6g). The mixture was stirred for 1 hour, neutralised by the addition of triethylamine and the mixture evaporated. The residue was partitioned between water (50ml) and dichloromethane (50ml). The organic extract was concentrated *in vacuo* and the residue

purified by chromatography (SiO_2, ethyl acetate:isohexane 1:2 as eluant) to afford the sub-title compound (3.0g).

MS (APCI) 500 ($M+H^+$, 100%).

b) (1*R-trans*)-1-Deoxy-2,3-*O*-(1-methylethylidene)-1-[7-(2-phenylcyclopropylamino)-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronic acid

A mixture of the product from step a) (3.0g) and pyridinium dichromate (30g) in dry dimethylformamide (30 ml) was stirred for 48 hours. The mixture was poured into water (500ml) and extracted with ethyl acetate, washed with 10% sodium metabisulfite solution. The organic layer was dried, concentrated *in vacuo* and the residue purified by reverse phase HPLC (NovapakC_{18}, acetonitrile:0.1% aqueous ammonium acetate, 35:65 as eluant) to afford the sub-title compound (2.1g).

MS (APCI) 513 ($M+H^+$, 100%).

c) [3aR-[3aα,4α,6α (1R*,2S*),6aα]]-2-Diazo-1-[2,2-Dimethyl-6-[7-(2-phenylcyclopropylamino)-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]tetrahydrofuro[3,4-d][1,3]dioxol-4-yl]ethanone

To an ice-cold mixture of the product from step b) (300mg) and *N*-methylmorpholine (0.059ml) in dry tetrahydrofuran (10 ml) was added isobutylchloroformate (0.076ml) dropwise. The mixture was allowed to attain room temperature and stirred for an additional 30 mins. This mixture was then added slowly to an ethereal solution of diazomethane (3.0g). After 1 hour the mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, dichloromethane as eluant) to afford the sub-title compound (0.3g).

MS (APCI) 509 ($M+H^+-N_2$, 100%).

d) (1*R-trans*)-1,5-Dideoxy-2,3-*O*-(1-methylethylidene)-1-[7-(2-phenylcyclopropyl)amino-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-*ribo*-hexofuranuronic acid, methyl ester

A mixture of the product from step c) (0.3g), methanol (50 ml) and silver (I) oxide (0.3 g) was heated under reflux for 8 hours. The reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The residue was purified by reverse phase HPLC (NovapakC$_{18}$, acetonitrile:0.1% aqueous ammonium acetate, 60:40 as eluant) to afford the sub-title compound (0.18g).

MS (APCI) 541 (M+H$^+$, 100%).

e) (1*R-trans*)-3-[5-Deoxy-2,3-*O*-(1-methylethylidene)-β-D-*ribo*-hexofuranosyl)]-*N*-(2-phenylcyclopropyl)-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

To an ice cooled solution of the product from step d) (0.18g) in toluene (10 ml) was added diisobutylaluminium hydride (1.5 M in toluene, 2.2 ml). The mixture was stirred for 30 min, quenched with water (1 ml), concentrated *in vacuo* and the residue purified by chromatography (SiO_2, dichloromethane as eluant) to afford the sub-title compound (0.085g).

MS (APCI) 513 (M+H$^+$, 100%).

f) (1*R-trans*)-3-[5-Deoxy-(β-D-*ribo*-hexofuranosyl)]-*N*-(2-phenylcyclopropyl)-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

A mixture of the product from step e) (85 mg), trifluoroacetic acid (0.1 ml) and water (0.01 ml) was stirred for 15 minutes. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, diethyl ether as eluant) to afford the title compound (0.035g).

MS (APCI) 473 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.41 (1H, d), 7.31-7.16 (5H, m), 6.05 (1H, d), 5.54 (1H, d), 5.23 (1H, d), 4.79-4.76 (2H, m), 4.47 (1H, t), 4.23 (1H, m), 4.08-4.05 (1H, m), 3.46-3.40 (2H, m), 3.19 (1H, m), 2.98-2.87 (2H, m), 2.15 (1H, m), 1.93-1.70 (2H, m), 1.54-1.47 (3H, m), 1.36-1.31 (1H, m), 0.82 (3H, t).

Example 8

(1*R-trans*)-1-Deoxy-1-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronic acid

A solution of the product from Example 7, step b) (0.41g) in trifluoroacetic acid (3.6ml) was treated with water (0.4ml) and allowed to stand at room temperature for 30 minutes. The mixture was diluted with ethyl acetate (300ml) and the solution stirred with a slight excess of cold, aqueous sodium bicarbonate solution. The mixture was acidified by addition of a slight excess of acetic acid, the ethyl acetate layer was separated, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, acetic acid:methanol:chloroform 1:6:93 as eluant) to afford the title compound (0.29g).

MS (APCI) 473 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.43 (1H, d), 7.32-7.16 (5H, m), 6.13 (1H, d), 5.76-5.72 (2H, m), 4.93-4.91 (1H, m), 4.63-4.61 (1H, m), 4.39 (1H, d), 3.22-3.20 (1H, m), 3.01-2.92 (1H, m), 2.88-2.79 (1H, m), 2.16-2.13 (1H, m), 1.54-1.30 (4H, m), 0.79 (3H, t).

Example 9

(1*R-trans*)-1-Deoxy-*N*-ethyl-1-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronamide

a) (1*R-trans*)-1-Deoxy-*N*-ethyl-2,3-*O*-(1-methylethylidene)-1-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronamide

To a solution of the product from Example 7, step b) (0.41g) in anhydrous tetrahydrofuran (10ml) was added benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (0.39g) followed by *N,N*-diisopropylethylamine (0.11g) and the resultant solution was stirred at room temperature for 40 minutes. The reaction mixture was then treated with a 70% solution of aqueous ethylamine (0.5ml) and stirring continued for a further 1 hour at room temperature. The mixture was neutralised by addition of acetic acid and then partitioned between ethyl acetate (200ml) and a saturated solution of aqueous sodium bicarbonate (200ml). The ethyl acetate layer was washed with brine (3 x 200ml) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, ethyl acetate:isohexane 2:3 as eluant) to afford the sub-title compound (0.39g).

MS (APCI) 540 ($M+H^+$, 100%).

b) (1*R-trans*)-1-Deoxy-*N*-ethyl-1-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronamide

A solution of the product from step b) (0.38g) in trifluoroacetic acid (3.6ml) was treated with water (0.4ml) and allowed to stand at room temperature for 30 minutes. The mixture was diluted with ethyl acetate (300ml) and the resultant solution washed with excess cold, saturated, aqueous sodium bicarbonate solution. The ethyl acetate layer was dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, methanol:chloroform 4:96 as eluant) to afford the title compound (0.21g).

MS (APCI) 500 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.51 (1H, d), 7.85 (1H, t), 7.32-7.16 (5H, m), 6.17 (1H, d), 5.75 (1H, d), 5.65 (1H, d), 4.83 (1H, q), 4.41-4.37 (1H, m), 4.33 (1H, d), 3.25-3.22 (1H, m), 3.16-

3.09 (2H, m), 2.95-2.90 (1H, m), 2.82-2.77 (1H, m), 2.15-2.11 (1H, m), 1.57-1.42 (4H, m), 0.99 (3H, t), 0.78 (3H, t).

Pharmacological data

The preparation for the assay of the P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor agonist/antagonist activity in washed human platelets for the compounds of the invention was carried out as follows.

Human venous blood (100 ml) was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as anti-coagulant. The tubes were centrifuged for 15 minutes at 240G to obtain a platelet-rich plasma (PRP) to which 300 ng/ml prostacyclin was added to stabilize the platelets during the washing procedure. Red cell free PRP was obtained by centrifugation for 10 minutes at 125G followed by further centrifugation for 15 minutes at 640G. The supernatant was discarded and the platelet pellet resuspended in modified, Calcium Free Tyrode solution (10 ml) (CFT), composition: NaCl 137mM, $NaHCO_3$ 11.9mM, NaH_2PO_4 0.4mM, KCl 2.7 mM, $MgCl_2$ 1.1 mM, dextrose 5.6 mM, gassed with 95% O_2/5% CO_2 and maintained at 37°C. Following addition of a further 300 ng/ml PGI_2, the pooled suspension was centrifuged once more for 15 minutes at 640G. The supernatant was discarded and the platelets resuspended initially in 10 ml CFT with further CFT added to adjust the final platelet count to $2x10^5$/ml. This final suspension was stored in a 60 ml syringe at 3°C with air excluded. To allow recovery from PGI_2-inhibition of normal function, platelets were used in aggregation studies no sooner than 2 hours after final resuspension.

In all studies, 3 ml aliquots of platelet suspension were added to tubes containing $CaCl_2$ solution (60 µl of 50 mM solution with a final concentration of 1mM). Human fibrinogen (Sigma, F 4883) and 8-sulphophenyltheophylline (8-SPT which was used to block any P_1-agonist activity of compounds) were added to give final concentrations of 0.2 mg/ml (60 µl of 10 mg/ml solution of clottable protein in saline) and 300 nM (10 µl of 15 mM solution in 6% glucose), respectively. Platelets or buffer as appropriate were added in a volume of 150 µl to the individual wells of a 96 well plate. All measurements were made in triplicate in platelets from each donor.

The agonist/antagonist potency was assessed as follows

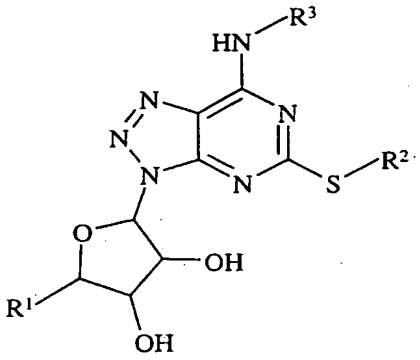
Aggregation responses in 96 well plates were measured using the change in absorbance given by the plate reader at 660 nm. Either a Bio-Tec Ceres 900C or a Dynatech MRX was used as the plate reader.

The absorbance of each well in the plate was read at 660 nm to establish a baseline figure. Saline or the appropriate solution of test compound was added to each well in a volume of 10 µl to give a final concentration of 0, 0.01, 0.1, 1, 10 or 100 mM. The plate was then shaken for 5 min on an orbital shaker on setting 10 and the absorbance read at 660 nm. Aggregation at this point was indicative of agonist activity of the test compound. Saline or ADP (30 mM; 10 µl of 450 mM) was then added to each well and the plate shaken for a further 5 min before reading the absorbance again at 660 nm.

Antagonist potency was estimated as a % inhibition of the control ADP response to obtain an IC_{50}. Compounds exemplified have pIC_{50} values of more than 5.0.

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is either alkyl C_{1-6} substituted by OH or COR^4;

R^2 is alkyl C_{1-6} or haloalkyl C_{1-6};

R^3 is cycloalkyl C_{3-6} optionally substituted by R^5;

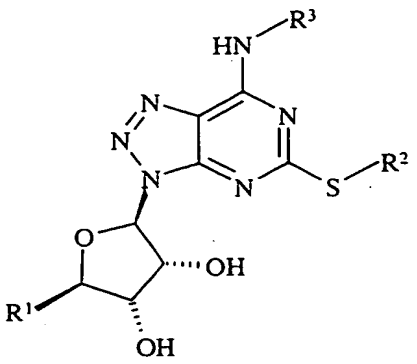
R^4 is OR^6 or NHR^6;

R^5 is phenyl optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen and OR^6;

R^6 is H or alkyl C_{1-6};

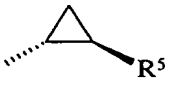
or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

2. A compound according to claim 1 which is:



(Ia)

where R^1, R^2 and R^3 are as defined in claim 1.

3. A compound according to claim 2 in which R^3 is  where R^5 is as defined in claim 1.

4. A compound according to any one of claims 1 to 3 in which R^1 is CH_2OH, $(CH_2)_2OH$, COOH or CONHEt.

5. A compound according to any one of claims 1 to 4 in which R^2 is alkyl C_3 optionally substituted by three halogen atoms.

6. A compound according to claim 1 which is:

(1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-[2-(4-Chlorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;

(1*R-trans*)-*N*-[2-(4-Fluorophenyl)cyclopropyl]-5-(propylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;
(1*R-trans*)-*N*-(2-Phenylcyclopropyl)-5-(3,3,3-trifluoropropylthio)-3-(β-D-ribofuranosyl)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;
(1*R-trans*)-3-(5-Deoxy-β-D-*ribo*-hexofuranosyl)-*N*-(2-phenylcyclopropyl)-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine;
(1*R-trans*)-1-Deoxy-1-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronic acid;
(1*R-trans*)-1-Deoxy-*N*-ethyl-1-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-β-D-ribofuranuronamide;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 in combination with a pharmaceutically acceptable diluent, adjuvent or carrier.

8. A pharmaceutical composition for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, comprising a compound according to any one of claims 1 to 6.

9. A pharmaceutical composition for use in the treatment or prevention of unstable or stable angina, comprising a compound according to any one of claims 1 to 6.

10. A compound according to any one of claims 1 to 6 for use in therapy.

11. A compound according to any one of claims 1 to 6 for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

12. A compound according to any one of claims 1 to 6 for use in the treatment or prevention of unstable or stable angina.

13. The use of a compound according to any one of claims 1 to 6 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

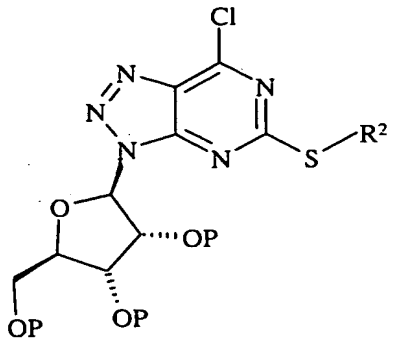
14. The use of a compound according to any one of claims 1 to 6 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of unstable or stable angina

15. A method of treatment or prevention of a platelet aggregation disorder which comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 6 to a person suffering from or susceptible to such a disorder.

16. A method of treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, which comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 6 to a person suffering from or susceptible to such a condition.

17. A method of treatment or prevention of unstable or stable angina which comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 6 to a person suffering from or susceptible to such a condition.

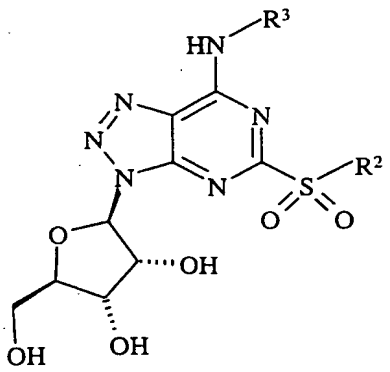
18. A process for the preparation of a compound of formula (I) where R^1 is CH_2OH, which comprises reacting a compound of formula (II):



(II)

where R^2 is defined in claim 1 and P is a protecting group, with R^3NH_2, where R^3 is defined in claim 1, and a base in the presence of dipolar aprotic solvent or an alcohol, at a temperature between about 100 and about 150°C, and optionally thereafter removing any protecting groups.

19. A process for the preparation of a compound of formula (I) where R^1 is CH_2OH, which comprises interconverting R^2 by reacting a compound of formula (VI):



(VI)

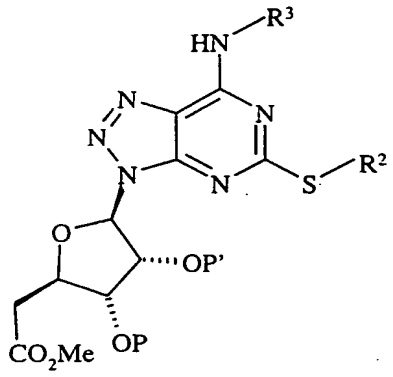
where R^2 and R^3 are as defined in claim 1,

i) with sodium hydrosulphide (NaSH) in the presence of a dipolar aprotic solvent, at a temperature between about 0 and about 50°C and treating the product of this reaction with

an alkyl halide ($R^{2'}X$) in the presence of a dipolar aprotic solvent, at a temperature between about 0 and about 50°C, or

ii) with a sodium alkylthiolate ($R^{2'}SNa$) in the presence of a dipolar aprotic solvent, at a temperature between about 0 and about 50°C, where $R^{2'}$ is different from the R^2 being interconverted.

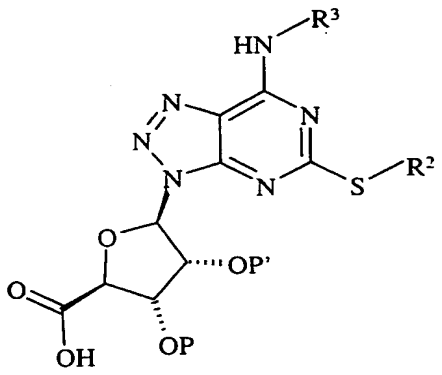
20. A process for the preparation of a compound of formula (I) where R^1 is $(CH_2)_2OH$, which comprises reducing a compound of formula (VIII):



(VIII)

where P and P' are protecting groups, and R^2 and R^3 are as defined in claim 1, with a metal hydride, in the presence of an inert solvent, at a temperature between about 0 and about 50°C and optionally thereafter removing any protecting groups.

21. A process for the preparation of a compound of formula (I) where R^1 is COOH, which comprises deprotecting a compound of formula (X):

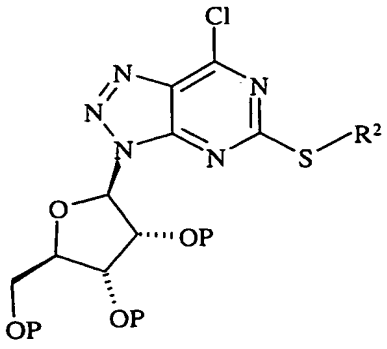


(X)

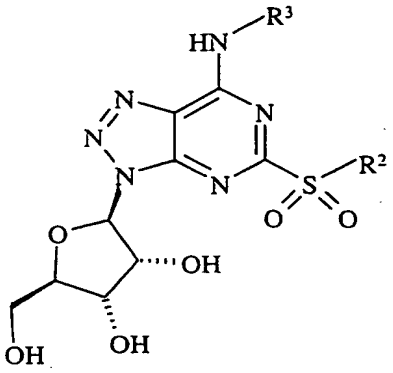
where P and P' are protecting groups, and R^2 and R^3 are as defined in claim 1, using an acid in water or aqueous acetonitrile, at a temperature between about 0 and about 100°C.

22. A process for the preparation of a compound of formula (I) where R^1 is $CONHR^6$, which comprises activating the carboxylic group of a compound of formula (X) as defined in claim 21, with a suitable activating reagent, and reacting the resultant compound with R^6NH_2, where R^6 is defined in claim 1, in the presence of a base in inert ethereal solvent, at a temperature between about 0 and about 50°C, and optionally thereafter removing any protecting groups.

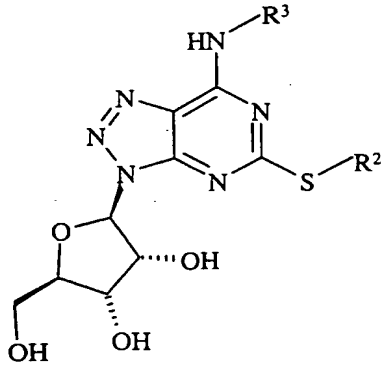
23. Compounds of formulae (II), (VI), (VII), (VIII) and (X):



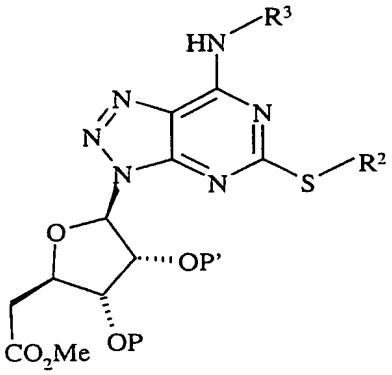
(II)



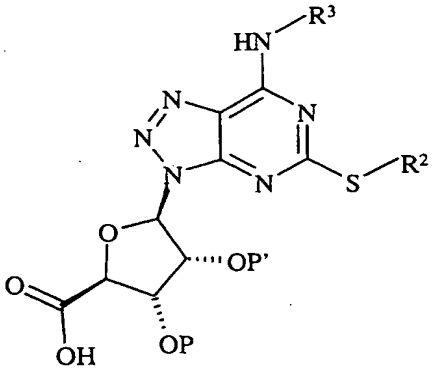
(VI)



(VII)



(VIII)



(X)

where P and P' are protecting groups, and R^2 and R^3 are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02230

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07H 19/04, A61K 31/7064, A61P 7/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9703084 A1 (ASTRA PHARMACEUTICALS LTD.), 30 January 1997 (30.01.97), page 4, line 1 - line 2; page 9, line 1 - line 7; the claims; the examples	1-23
X	WO 9905143 A1 (ASTRA PHARMACEUTICALS LTD.), 4 February 1999 (04.02.99)	1-23
A	WO 9828300 A1 (ASTRA PHARMACEUTICALS LTD.), 2 July 1998 (02.07.98)	1-23
A	WO 9905142 A1 (ASTRA PHARMACEUTICALS LTD.), 4 February 1999 (04.02.99)	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2001	08 -02- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02230

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15-17
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02230

Claims 15-17 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/02230

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703084 A1	30/01/97	AU 699034 B	19/11/98
		AU 6375196 A	10/02/97
		BR 9609467 A	02/03/99
		CA 2226758 A	30/01/97
		CN 1195353 A	07/10/98
		CZ 9800025 A	12/08/98
		EP 0840740 A	13/05/98
		GB 9514074 D	00/00/00
		HU 9802448 A	28/05/99
		IL 122814 D	00/00/00
		JP 11508914 T	03/08/99
		NO 980080 A	06/03/98
		NZ 312258 A	30/08/99
		PL 324396 A	25/05/98
		SK 2398 A	11/01/99
		US 5747496 A	05/05/98
		ZA 9605905 A	13/01/97
		GB 9520311 D	00/00/00
		GB 9522837 D	00/00/00
WO 9905143 A1	04/02/99	AU 8370698 A	16/02/99
		BR 9810802 A	12/09/00
		CN 1270590 T	18/10/00
		EP 0996621 A	03/05/00
		NO 20000312 A	21/03/00
		SE 9702773 D	00/00/00
		SE 9702775 D	00/00/00
		ZA 9806050 A	06/04/99
WO 9828300 A1	02/07/98	AU 5501598 A	17/07/98
		EP 0946561 A	06/10/99
		SE 9604787 D	00/00/00
		SE 9604788 D	00/00/00
WO 9905142 A1	04/02/99	AU 8370598 A	16/02/99
		BR 9811022 A	12/09/00
		CN 1271359 T	25/10/00
		EP 0996620 A	03/05/00
		NO 20000311 A	21/03/00
		SE 9702772 D	00/00/00